REMARKS

Knockout mouse models have been relied upon for decades as being indicative of the participation of a given gene in a disease process or phenotype. Applicant has made a significant contribution to the field of diabetes by identifying a gene marker for insulin resistance, and indeed, a gene involved in the pathology of the disease. A reduction in Mal1 expression (as demonstrated using a Mal1-deficient gene knockout mouse) was found to correlate with an improvement in insulin sensitivity (i.e., a decrease in insulin resistance). These data formed the basis for claims directed to diagnosing the condition of insulin resistance (or a means by which to predict a risk of developing such a condition) by measuring Mal1 levels. Applicant has now confirmed the reliability and efficacy of the claimed methods by showing that an increase in Mal1 expression (using a Mal1 transgenic mouse that expresses high levels of Mal1) correlates with insulin resistance (i.e., reduced insulin sensitivity). The "loss-of-function" and "gain-of-function" data are in complete agreement and confirm the scientific basis and reliability of the claimed methods.

Upon entry of the present amendment, claims 16, 22-24, 27, and 31-36 are pending in the application. Claims 16 and 35 were amended to delete the phrase "at least 10 nucleotides", and claim 27 was amended to put it into independent form.

No new matter has been added by this amendment.

I. Rejections under 35 U.S.C. § 112, second paragraph

Claim 27 was rejected for indefiniteness for depending from a canceled claim. This claim has been amended to put it into independent format.

II. Rejections under 35 U.S.C. § 112, first paragraph

Claims 16, 22-24, 27 and 35 were rejected for lack of written description. On page 3, lines 10-18, of the Office Action, the Examiner states:

> The specification and claims do not indicapte which nucleotides (i.e., 10 nucleotides) of SEQ ID Nos: 4 or 2 are specifically representative of Mal1 transcript expression and do not share homology with other iLBP family members. The scope of the claims reads on numerous structural variants and specific, not general, guidance is needed to determine which minimum of 10 nucleotides of SEQ ID Nos: 4 or 2 specifically indicates and (sic) increase in Mal1 transcript. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus comprising a 10 nucleotide transcript (of SEQ ID Nos:2 or 4) that specifically represents Mal1 transcript expression.

Claim 16 has been amended to require that the Mal1 transcript contain the nucleotides defined by SEQ ID NO:4. Claim 27 requires nucleotides 49-456 of SEQ ID NO:4. Claim 35 has been amended to require SEQ ID NO:2. In view of these amendments, this ground of rejection should be withdrawn.

Claims 16, 22-24, 27, and 31-36 were also rejected for overbreadth and lack of enablement. On page 5, lines 7-18, of the Office Action, the Examiner states:

> The specification teaches a correlation between genetic ablation of Mal1 in mice and decreases in body weight, reduction in circulating lipids and increased systemic insulin sensitivity. One skilled in the art would not accept on its face the examples given in the specification of the observed decreases in body weight or circulating lipids, and increased systemic insulin sensitivity, as being correlative or representative of the successful diagnosis of a subject at risk of developing insulin resistance comprising a comparison of expression of Mal1. The specification as filed failed to provide any particular guidance which resolves the known unpredictability in the art associated with the ability to quantitate and compare expression of Mal1 transcripts or polypeptides in a normal human or mouse with one at risk of developing insulin resistance. Furthermore, the ability to assay differences in Mal1 transcript expression comprising measuring at least 10 nucleotides of said transcript involves an assay that specifically measures Mal1 transcript. Since the prior art teaches extensive sequence similarity between various iLBP family members, it would require undue experimentation to determine which transcript comprising 10 nucleotides would specifically reflect an increase in Mal1 transcript expression, as opposed to an increase in other iLBP family members.

As is discussed above, the claims have been amended to require determining the level of a Mal1 transcript containing the nucleotide sequence of SEQ ID NO:4 (claim 16), nucleotides 46-456 of SEQ ID NO:4 (claim 27), nucleotide sequence of SEQ ID NO:2 (claim 35) or the amino acid sequence of SEQ ID NO:3 or 1 (claims 31 and 36, respectively). As amended, the claims specifically reflect an increase in Mal1 transcript expression, as opposed to an increase in other iLBP family members.

With respect to predictability, the Examiner has given no evidence as to why one skilled in the art would not accept on its face the examples given in the specification of the observed decreases in body weight or circulating lipids, and increased systemic insulin sensitivity, as being correlative or representative of the successful diagnosis of a subject at risk of developing insulin resistance. The correlation of reduced Mal1 with insulin sensitivity is shown in Figs. 4 and 5 (standard insulin tolerance test and glucose tolerance test, respectively) of the application. These assays represent widely accepted clinical tests for the evaluation of insulin resistance. The data firmly establish the correlation between the level of Mal1 and the insulin resistance.

Numerous studies have since confirmed the teachings of the specification regarding the correlation between the level of Mal1 and insulin resistance. For example, the correlation between the level of Mal1 expression and insulin resistance was confirmed in yet another relevant animal model, obese mice lacking the gene aP2 (Uysal et al., 2000, Endocrinology 141:3388-3396; submitted with amendment file in April 2002). These mice found to be protected from insulin resistance, i.e., $aP2^{-/-}$ mice had better performance in insulin and glucose tolerance tests compared to obese $aP2^{+/+}$ mice. Confirming the teachings of the originally-filed specification, these mice were also found to have significantly reduced levels of Mal1 expression. In yet another publication (Maeda et al., 2003, Diabetes 52:300-307; attachment A), Applicant shows that "absence of mal1 resulted in increased insulin sensitivity in two models of

obesity and insulin resistance" (see abstract) using mal1-deficient mice. Moreover, in gain-of-function experiments using mal1 trangenic mice in which high levels of mal1 transgene were produced under the control of a strong promoter, reduced systemic insulin sensitivity (insulin resistance) was observed. The phenotype of the Mal1transgenic mice with overexpression of Mal1 demonstrated a phenotype opposite that of the loss of function (mal1 -/-) model (abstract and page 306, column 1, lines 9-23 of Maeda et al.). These data confirm the predictability that an increase in Mal1 expression is indicative of insulin resistance or a risk of developing such a condition. In view of the disclosure provided in the originally-filed specification, confirmation of the teachings regarding Mal1 levels and insulin resistance, and the ample guidance in the specification regarding how to measure Mal1 transcription (SEQ ID NO: 4 or 2) or Mal1 protein (SEQ ID NO:3 or 1), Applicant respectfully requests withdrawal of this rejection.

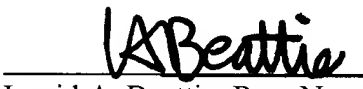
CONCLUSION

Applicant submits that the application is in condition for allowance and such action is respectfully requested.

A petition for extension of time and a check in the amount of $950.00 is enclosed to cover the petition fee for a three-month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No.21509-044.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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